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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
09/021,660	02/10/98	BARON	M 1877-110

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EXAMINER	
ART UNIT	PAPER NUMBER
1646	10

DATE MAILED: 09/22/99

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

1 - PATENT APPLICATION FILE COPY

PTOL-90 (Rev. 6/84)

Office Action Summary	Application No. 09/021,660	Applicant(s) Baron et al.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *06 July 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *27-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-56* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☒ Notice of References Cited (PTO-892)
15) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

The preliminary amendment filed June 1, 1999 has been entered.

The CRF has been corrected by the US PTO STIC staff so that non-ASCII "garbage" at the end of the files was deleted. This information is provided for Applicants' knowledge and no action by Applicants needs to be taken.

Election/Restrictions

Applicant's election of Invention I in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The filing date of priority provisional application 60/049,763 listed as Sept. 9, 1997 is incorrect. The correct filing date is June 16, 1997. A substitute declaration is required to correct this error.

Incorporation by Reference

The attempt to incorporate subject matter into this application by reference to foreign applications may be improper if these publications contain essential material. An application for a patent when filed may incorporate "essential material" by reference to (1) a U.S. patent or (2) an allowed U.S. application in which the issue fee has been paid, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best

mode (35 U.S.C. 112). In any application which is to issue as a U.S. patent, essential material may **not** be incorporated by reference to (1) patents or applications published by foreign countries or a regional patent office, (2) non-patent publications, (3) a U.S. patent or application which itself incorporates "essential material" by reference, or (4) a foreign application. See In re Fouche , 439 F.2d 1237, 169 USPQ 429 (CCPA 1971).

If, however, the publications listed contain only nonessential subject matter, that matter may be incorporated by reference. Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art.

Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. In re de Seversky , 474 F.2d 671, 177 USPQ 144, (CCPA 1973). In addition to other requirements for an application, the referencing application should include an identification of the referenced patent, application, or publication. Particular attention should be directed to specific portions of the referenced document where the subject matter being incorporated may be found

If the Applicants intend to incorporate essential subject matter from the listed publications by reference, the disclosure must be amended to include the material incorporated by reference. The amendment must be accompanied by an affidavit of declaration executed by the applicant, or applicant's attorney or agent, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157; *In re Hawkins*, 486 F.2d 579, 179 USPQ 163; *In re Hawkins*, 486 F.2d 577, 179 USPQ 167. If, however, the subject matter is nonessential and the Applicants wish to incorporate the listed publications by reference, then specific pertinent portions of the publications must be identified.

If the claims are intended to encompass, for example, hedgehog homologs disclosed in WO 95/18856 (page 22, line 18), the structure of those homologs would be essential matter and the WO application not incorporatable by reference.

Sequences

This application contains sequence disclosures that are encompassed by the definitions for nucleic and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth in the attached Notice to Comply with Requirements for Patent Applications Containing Nucleic Sequence and/or Amino Acid Sequence Disclosures. In the current application, all sequences appearing (nucleic acid sequences over 10 nucleotides long) must be in the CRF and paper copy of the Sequence Listing. It appears there may be sequences not included (see next paragraph).

According to 37 CFR 1.821(d) (MPEP ' 2422), where the description or claims of a patent application discuss a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the assigned identifier, in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. Sequences appearing in the specification must be referred to by an assigned identifier (*e.g.*, page 32, lines 17-19, page 39, lines 14-33, page 41, line 25 through page 42, line 2, page 49, lines 1-7).

Drawings

Figure 1 of the instant application is presented on four separate panels. 37 C.F.R. § 1.84 (u)(1) states that when partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a **capital** letter. The three sheets of drawing which are labeled "Figure 1" in the instant specification should be renumbered "Figure 1A, 1B, and 1C". Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84 (u)(1), Applicant is required to change the Brief Description of the Drawings and the rest of the specification accordingly. Figure 1 is followed by lower case not capital letters. Also, the Brief Description and all references to this figure in the specification must refer to Figures 1A, 1B, 1C and/or 1D as appropriate (*e.g.*, page 6, line 7). The same is true for other figures presented on

separate panels. For example Figure 7a-d and Figure 7-1(a)-(e) could be referred to as Figure 7A1-7A4 and Figures 7B1-7B5 or, more preferably, Figures 7A-7D and Figures 8A-8E.

Specification

The disclosure is objected to because of the following informalities: on page 3, end of line 12, the period should be a comma, and on line 24 of the page, "hematopoletic" should be --hematopoietic--; page 10, line 2, "deficient." should be --deficient,--; page 18, line 4, there are two periods after "identified"; page 31, line 10, there should be a close parenthesis around "(MB72"; page 37, line 23, no period.

Appropriate correction is required.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Objections

Claim 8 are objected to because of the following informality: Claim 8 should end with a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 9-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant specification describes three hedgehog proteins (Ihh, Shh and Dhh) and one TGF-ß family member which is BMP-4 that can stimulate undifferentiated mesodermally derived cell to under hematopoiesis. The specification describes no compounds that stimulate the cells to undergo vascular growth. It is noted that expression of an endothelial marker (*e.g.*,

flk-1) does not indicate that vascular growth has been stimulated. Vascular growth is a further differentiation of endothelial cells for which the markers do not provide evidence. However, the claims are directed to or encompass a diverse array of compounds, which may or may not be proteins, that have the recited hematopoietic or vascular growth property. Not only is any compound that is a gene product expressed in an embryo's extraembryonic tissue and has one of the properties encompassed, but also encompassed is any compound functionally equivalent to a compound that is a gene product expressed in extraembryonic tissue. None of these undisclosed compounds meets the written description provision of 35 USC 112, first paragraph. Disclosure of assays or systems one could use to identify compounds in addition to the ones disclosed is an invitation to experiment without a reasonable expectation of success and does not support written description for the undisclosed compounds.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.* (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the specific proteins referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only naturally occurring hedgehog proteins and BMP-4, but not the full breadth of the claim meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 1-26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The invention is drawn to a method of stimulating a population of undifferentiated mesodermally derived cells (*e.g.*, hematopoietic stem cells, yolk sac mesoderm) to undergo hematopoiesis or vascular growth by a compound which has accessed the cells. The compound must be "functionally equivalent to a gene product expressed in an embryo's extraembryonic tissue" according to claim 1. The prior art teaches that BMP-4 and to a lesser extent BMP-2 when introduced into *Xenopus* oocytes cause formation of blood cells (Hemmati-Brivanlou et al., U, Dev. Genet., 1995, see below). Dickson et al. (AX, Dev., 1995) showed that TGF-ß1 is necessary for both proper vasculogenesis and hematopoiesis, particularly in differentiation of yolk sac mesoderm. Even though a common molecule can *influence* both vasculogenesis and hematopoiesis, these are distinct events affecting distinct cell types. Other molecules, such as VEGF are active in vasculogenesis but not hematopoiesis (*e.g.*, Carmeliet et al., AO, Nature, 1996, and Moses, DJ, Int. Re. Cytol., 1995). Also taught in the prior art is the native receptor of hedgehog called patched (ptc, *e.g.*, Goodrich et al., BW, Genes Dev., 1996). It is acknowledged

that relative skill of those in the art relating to what tissues give rise to hematopoiesis and what markers are indicative of hematopoiesis is high; however, the skill of those in the art is not high concerning which compounds induce or might induce hematopoiesis. While there are suggestions in the art of compounds which might induce hematopoiesis, the predictability about whether or not those compounds actually can is low. For example, it has been shown that mice embryos deficient in the flk-1 receptor (*i.e.*, a receptor for VEGF) have severely reduced hematopoiesis and vasculogenesis (Shalaby et al., EI, Nature, 1995). Nevertheless, it has not been shown that VEGF itself can induce hematopoiesis, although it has clearly been shown to induce vasculogenesis. For vascular growth it was known that presumptive endothelial cells give rise to blood vessels; however, the markers for endothelial cells alone will not distinguish those cells which will specifically form blood vessels (*e.g.*, flk-1). It does not appear that at the time the invention was made there were definitive markers for vascular endothelial cells. While prior art compounds were shown to induce vascular growth, the predictability about whether a compound not previously known to have that function could induce vascular growth of undifferentiated mesodermally derived cells was low.

It appears that the method of claim 1 and some dependent claims (*e.g.*, claim 24) include techniques involved in gene therapy and transgenic expression--as the compound must "access the cells", which could include intracellular translation of a nucleic acid encoding a protein which is the compound. This method is extremely unpredictable and has no support in the prior art for wide application of the method. There is no showing in the specification that such translation would be possible within a cell in an animal. The are examples in the specification of the absence of compounds in transgenic animals, but not the addition of or additional expression of compounds that can induce hematopoiesis or vascular growth. There is insufficient guidance to allow the skilled artisan to practice the method by this manner with a reasonable expectation of success and without undue experimentation.

The instant application has no working examples of stimulating undifferentiated mesodermally derived cells to undergo vascular growth. Nor are there examples of any compounds other than Shh, Ihh or BMP-4 stimulating the cells to undergo hematopoiesis.

However, studies using Ihh and Dhh knockout transgenic mice would lead the skilled artisan to reasonably expect that Dhh could also be used in the claimed method (see page 20-21). There are no examples in the specification or prior art of a hedgehog protein binding to and activating any receptor other than ptc. There is no evidence in the prior art or instant specification that a Drosophila hedgehog polypeptide can activate a vertebrate patched receptor or *vice versa*.

The claims as written have great breadth in terms of stimulation of hematopoiesis or vascular growth. It is noted that expression of an endothelial marker does not indicate that vascular growth has been stimulated.. This is a further differentiation of endothelial cells for which the markers do not provide evidence. On the other hand, the breadth of the claims added by the types of cells that may be undifferentiated mesodermally derived cells is *not* great since the developmental lineage of such cells has been well known in the art and the specification provides guidance and examples of the types of cells that can be successfully used in the claimed method. Nevertheless, breadth is added by what the compound can be. In claim 1, the only limitation attached to the compound is that it be "functionally equivalent to a gene product expressed in an embryo's extraembryonic tissue". That is, the compound does not have to be a gene product expressed in extraembryonic tissue. It is noted that in the specification, a "hedgehog compound" is defined as a hedgehog protein or analog or derivative thereof or agonists or antagonists of hedgehog protein receptors of functional equivalents of any of these. Therefore, such a compound need not have any resemblance to a naturally occurring Ihh, Dhh or Shh polypeptide. Also, according to claim 10, the compound can be a "functional equivalent of a TGF-ß family member". In terms of the compounds that can be used, including the functional equivalents, the claims are single means claims (see MPEP 2164.08), i.e., where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph. In re Hyatt, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983) (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor.). When claims depend on a recited property, a fact situation comparable to Hyatt is possible, where the claim covers

every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. Further, defining a polypeptide by its activity is analogous to the situation argued for DNA defined by the activity of the polypeptide it encodes as put forth in *Ex parte Maizel* (27 USPQ2d 1662 at 1665):

> Appellants have not chosen to claim the DNA by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, *or* a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt*, 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it cover any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses at most, only the specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claim."

In the current case, the compound is being defined by what functional property it has, not by what it is. Disclosure of assays or systems (*e.g.*, transgenic mice) one could use to identify compounds is an invitation to experiment without a reasonable expectation of success and does not support enablement for the scope of undisclosed compounds.

For claim 9 and dependent claims, the first compound must be capable of acting synergistically with a second compound. The specification on page 11, line 20, defines a "Synergist effect" as "for two or more compounds where little or no biological effect is observed with the compounds alone but together the compounds have a potent biological effect." There is no teaching in the specification or the prior art of such compounds capable of having one of the required effects together where each compound alone as little or not effect.

For these reasons, it would require undue experimentation to practice the invention commensurate in scope with the broad claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and dependent claims 2-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it is unclear what is meant by "causing the compound to access the cells". For example, Shh does not normally enter a cell, but acts by binding its receptor on the cell surface. It is unclear if this is intended to qualify as "accessing the cells". Additionally, it is unclear if the phrase is meant to include accessing by internal expression of the protein from a nucleic acid, such as would need to occur in gene therapy or transgenic compound-expressing animals (for which the instant application is not enabled, see preceding section).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 14, 15, 20 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Hemmati-Brivanlou et al. (U, Dev. Genet., 1995).

Hemmati-Brivanlou et al. teach stimulating a population of undifferentiated mesodermally derived cells to undergo hematopoiesis by causing BMP-4 to access the cells by injecting *Xenopus* oocytes with encoding mRNA (p. 80, second paragraph; p. 81, last paragraph; and p. 84, paragraph bridging cols. 1-2). BMPs are secreted proteins and, therefore, are provided in the culture medium.

Claims 1-4, 14-16, 20, 24 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Zeigler et al. (V, Blood, 1994).

Zeigler et al. teach stimulating a population of undifferentiated mesodermally derived cells (hematopoietic stem cells including fetal liver cells) to undergo hematopoiesis by applying TPO to the cells (p. 4049, col. 1). TPO is a secreted protein and was effective when added to the culture medium (middle of second paragraph on p. 4049).

Note that since the specification broadly defines a hedgehog compound (including functional equivalents), and BMP-4 and TPO are receptor ligands which qualify as "hedgehog compounds", then they also are agonists of a hedgehog protein binding receptor.

Claims 1-2, 12 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Carmeliet et al. (AO, Nature, 1996).

Carmeliet et al. teach stimulation of a population of undifferentiated mesoderm cells to undergo vascular growth by causing VEGF to enter the cells by making embryos which express VEGF (VEGF +/+). Vasculogenesis was shown by the presence of dorsal aorta and head vessels (sentence bridging pages 437-438). The amount of vascular growth was decreased in embryos with inactivated VEGF (VEGF +/- and VEGF -/-, page 436, col. 2, and paragraph bridging pages 437-438). VEGF is a secreted protein. It was active on cells, included cells of the visceral endoderm (see legend of TABLE 1).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

September 21, 1999